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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WYETH
PATENT LAW GROUP
5 GIRALDA FARMS
MADISON, NJ 07940

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/699,874	KUNZ ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *113-127,129-135 and 142-149* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *113-127,129-135 and 142-144* is/are rejected.

7)☒ Claim(s) *145-149* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/27/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The Amendment filed on 5/16/2007 in response to the Non-Final Office Action (8/17/2006) is acknowledged and has been entered.

Claims 113-127, 129-135 and 142-149 are currently pending.and under consideration.

Information Disclosure Statement

The Information Disclosure Statement filed on 3/27/2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Rejections Withdrawn:

The rejection of claim 144 under 112, 2nd paragraph, as being vague and indefinite for reciting the term CMC-544 as the sole means of identifying the claimed molecule is withdrawn in view of Applicants amending the claim to recite G5/44-NAc-gamma-calicheamicin DMH AcBut conjugate.

The rejection of claims 113-123 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants amending the claims to recite a CD22 antibody.

The rejection of claims 113-123 under 35 U.S.C. 112, first paragraph enablement is withdrawn in view of Applicants amending the claims to recite a cytotoxic derivative conjugated to an anti-CD22 antibody.

The rejection of claims 113-116 and 122-123 are rejected under 35 U.S.C. 102(b) as being anticipated by Hellstrom et al. (US 5,134,075, 1992) is withdrawn in view of Applicants amending the claims to recite an anti-CD22 antibody which is not taught by Hellstrom.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 113 remains rejected under 35 U.S.C. 102(b) as being anticipated by Ghetie et al. (Blood 1992; 80: 2315-2320, of record) as evidenced by Newton et al. (Blood 2001; 97: page 528-535, of record).

Ghetie et al. teach a method of treating a lymphoma, comprising administering a therapeutically effective amount of a cytotoxic drug/carrier conjugate referred to as RFB4-dgA, wherein the cytotoxic drug is deglycosylated ricin A chain and the carrier is an antibody directed against the CD22 antigen (page 2317, , 1st column, 2nd to last sentence bridging 2nd column and Table 3). Moreover, the reference teaches a method of treating disseminated Daudi lymphoma comprising administering a therapeutically effective amount of the immunologic conjugate RFB4-dgA with an antibody directed against the CD19 antigen, wherein the combination of the anti-CD19 antibody and immunologic conjugate had significant antitumor activity (abstract and page 2318, Table 6). With regards to the administration, Ghetie et al. teach that the immunologic conjugate was administered retroorbitally (page 2316, 1st column, *IT therapy*). Thus, while Ghetie et al. do not explicitly teach that Daudi lymphoma is a B cell malignancy, the claimed limitation does not appear to result in a manipulative difference in the prior arts method because as evidenced by Newton et al. Daudi lymphoma are human B-cell tumors (page 531, 1st column, 2nd full paragraph). See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

In response to this rejection, Applicants contend that Ghetie et al. does not teach the instantly claimed invention of Claim 113 which specifically recites the steps by which the monomeric cytotoxic drug/carrier conjugate is prepared; and therefore, does not teach every element of the claimed invention in claim 113.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertions that Ghetie et al. does not teach the process steps of preparing the monomeric cytotoxic drug/carrier conjugate, the Examiner acknowledges and agrees with Applicants that Ghetie does not specifically teach the process steps involved in the synthesis of the monomeric cytotoxic drug/carrier conjugate. However, the Examiner recognizes that while the claims recite the process steps by which the monomeric cytotoxic drug/carrier conjugate is produced; the claims encompass a method of treating a proliferative disorder in a subject comprising administering to said subject a monomeric cytotoxic drug/carrier conjugate. As such, the Examiner has interpreted the process step by which the monomeric cytotoxic drug/carrier conjugate is produced in a similar manner to a product by process claim, wherein "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted), see MPEP 2113 [R1].

Claims 113-121 remain rejected under 35 U.S.C. 102(b) as being anticipated by Uhr et al. (US 5,686,072, 1997, of record).

Uhr et al. teach a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of a combination of an anti-CD19 antibody and anti-CD22 immunotoxin, wherein the B cell malignancy includes, but is not limited to, leukemia and non-Hodgkin's lymphoma (column 2, lines 48-54 and column 6, lines 16-21). With regards to the patient, the patent teaches that the patients include, but are not limited to, humans (column 6, lines 56-57). With regards to the administration, the patent teaches that the combination can be administered intravenously (column 12, lines 1-2).

In response to this rejection, Applicants assert that Ur et al. does not teach the steps by which the monomeric cytotoxic drug/carrier conjugate is prepared and therefore does not teach every limitation of the claimed invention in claims 113-121.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertions that Ur et al. does not teach the process steps of preparing the monomeric cytotoxic drug/carrier conjugate, the Examiner acknowledges and agrees with Applicants that Ur et al. does not specifically teach the process steps involved in the synthesis of the monomeric cytotoxic drug/carrier conjugate. However, the Examiner recognizes that while the claims recite the process steps by which the monomeric cytotoxic drug/carrier conjugate is produced, the claims encompass a method of treating a proliferative disorder in a subject comprising administering to said subject a monomeric cytotoxic drug/carrier conjugate. As such, the Examiner has interpreted the process step by which the monomeric cytotoxic drug/carrier conjugate is produced in a similar manner to a product by process claim, wherein "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted), see MPEP 2113 [R1].

Claims 113-121 remain rejected under 35 U.S.C. 102(b) as being anticipated by Goldenberg (US 6,183,744, 2001, cited in the previous Office Action as US 6,183,477).

Goldenberg teaches a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent (column 4, lines 25-26 and column 11, lines 5-8). For example, the patent teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (column 11, lines 11-14). In addition to Non-Hodgkin's lymphoma, the patent teaches that the immunoconjugates are useful for the treatment of chronic lymphatic leukemias, and acute lymphatic leukemias (column 11, lines 8-11). Regarding the therapeutic agent of the immunoconjugate, the patent teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes and folic acid analogs (column 12, lines 61+).

With regards to the administration, the patent teaches that the immunoconjugates can be administered intravenously (column 14, lines 8-15).

In response to this rejection, Applicants assert that Goldenberg et al. does not teach the steps by which the monomeric cytotoxic drug/carrier conjugate is prepared and therefore does not teach every limitation of the claimed invention in claims 113-121. The rest of Applicants arguments pertaining to the rejection of claims 124-127, 131-134 and 142, which has been withdrawn in view of Applicants amendments, but will be discussed in more detail below (103 rejection below).

These arguments have been carefully considered, but are not found persuasive.

First, the Examiner would like to thank Applicants for pointing out the error in the citation of Goldenberg and has corrected this error as noted above. Regarding Applicants assertions that Goldenberg et al. does not teach the process steps of preparing the monomeric cytotoxic drug/carrier conjugate, the Examiner acknowledges and agrees with Applicants that Goldenberg et al. does not specifically teach the process steps involved in the synthesis of the monomeric cytotoxic drug/carrier conjugate. However, the Examiner recognizes that while the claims recite the process steps by which the monomeric cytotoxic drug/carrier conjugate is produced, the claims encompass a method of treating a proliferative disorder in a subject comprising administering to said subject a monomeric cytotoxic drug/carrier conjugate. As such, the Examiner has interpreted the process step by which the monomeric cytotoxic drug/carrier conjugate is produced in a similar manner to a product by process claim, wherein "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted), see MPEP 2113 [R1].

New Rejections Necessitated by Amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 144 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear whether a cell line which produces an antibody having the exact chemical identity of 5/44, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one or ordinary skill in the art could not be assured of the ability to practice the claimed invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3rd ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species 5/44. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See, 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make

such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;
(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;
(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and
(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an addition means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claims 113-116 and 122-123 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a subject with a B-cell malignancy such as leukemia or lymphoma comprising administering a therapeutically effective dose of a composition comprising a therapeutically effective dose of a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate, does not reasonably provide enablement for a method of treating a subject with any and/or all cancers including, but not limited to, sarcoma or carcinomas comprising administering a therapeutically effective dose of a monomeric cytotoxic drug deriviative/anti-CD22

antibody conjugate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination

of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of treating cancer in a mammal comprising administering a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of treating a subject with a proliferative disorder comprising administering a therapeutically effective dose of a monomeric cytotoxic drug deriviative/anti-CD22 antibody conjugate. The claims are further drawn to the proliferative disorder being cancer, wherein the cancer includes, but is not limited to, carcinomas and sarcomas as the proliferative disorder.

Guidance in the specification and Working Examples

The specification teaches that conjugates of the invention comprise a cytotoxic drug derivatized with a linker that is reactive with a proteinaceous carrier to form a cytotoxic drug derivative-proteinaceous carrier conjugate (page 21, lines 3-5). The specification further teaches that proteinaceous carriers include antibodies which are reactive against a cell surface antigen on B-cell malignancies (page 21, lines 9-10). For example, the specification teaches that antibodies reactive with B-cell malignancies include, without limitation, antibodies directed against CD22 such as G5/44 which is over-expressed on most B-cell lymphomas (page 22, lines 25-27). As such, the specification teaches that the these antibody conjugates are useful for the treatment of proliferative disorders namely lymphomas and leukemias, which express CD22 antigen on the cell surface; and further, provides a plethora of lymphomas and leukemias contemplated for treatment (page 40, lines

1-20). Thus, while the specification reasonably conveys a method of treating a proliferative disorder namely lymphoma or leukemia which express a CD22 antigen with the anti-CD22 conjugate, the specification appears to be silent on a correlation between the anti-CD22 antibody conjugate and the treatment of any and/or all cancers including carcinomas and sarcomas. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of cancer therapy is extremely large given the unpredictability associated with treating cancer in general and the lack of correlation of in vitro findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that anti-CD22 antibodies, as well as the immunoconjugates thereof, are useful for the treatment of B-cell malignancies. For example, Goldenberg et al. (US 6,183,744, 2001) teaches a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent (column 4, lines 25-26 and column 11, lines 5-8). Moreover, Goldenberg teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (column 11, lines 11-14). In addition to Non-Hodgkin's lymphoma, Goldenberg et al. teaches that the immunoconjugates are useful for the treatment of chronic lymphatic leukemias, and acute lymphatic leukemias (column 11, lines 8-11). Similarly, Uhr et al. (US 5,686,072, 1997, of record) teach a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of a combination of an anti-CD19 antibody and anti-CD22 immunotoxin, wherein the B cell malignancy includes, but is not limited to, leukemia and non-Hodgkin's lymphoma (column 2, lines 48-54 and column 6, lines 16-

21). Thus, while the state of the prior art suggests a correlation with CD22 and B-cell malignancies, the prior art appears to be silent on CD22 expression being associated with carcinomas and sarcomas.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 124-127, 129-133 and 142-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldenberg (US 6,183,744, 2001), as applied to claims 113-121 above, in view of Trail et al. (Current Opinion in Immunology 1999, 11: 584-588, of record).

Goldenberg teaches a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent (column 4, lines 25-26 and column 11, lines 5-8). For example, the patent teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (column 11, lines 11-14). In addition to Non-Hodgkin's lymphoma, the patent teaches that the immunoconjugates are useful for the treatment of chronic lymphatic leukemia's, and acute lymphatic leukemia's (column 11, lines 8-11). Regarding the therapeutic agent of the immunoconjugate, the patent teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs pyrimidine analogs, purine

analogs, antibiotics, epipodophyllotoxins, platinum coordination complexes and hormones (column 12, lines 61+). With regards to the administration, the patent teaches that the immunoconjugates can be administered intravenously (column 14, lines 8-15).

Goldenberg does not explicitly teach that the therapeutic agent portion of the conjugate is the antibiotic, calicheamicin.

Trail et al. teach monoclonal antibody drug conjugates in the treatment of cancer. Specifically, the reference teaches that members of the enediyne family of antibiotics such as calicheamicin are among the most toxic antitumor compounds described to date, but there utility as antitumor dugs has-for the most part-been limited by their low therapeutic index (page 584, 2nd column, last sentence to page 585, 1st column). Trail et al. further teach that anti-body directed delivery provides a potential means to exploit the impressive potency of these compounds while minimizing their systemic toxicity (page 585, 1st column, 1st paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use calicheamicin, a species of antibiotics, in the method taught by Goldenberg in view of Trail et al. teachings that calicheamicin are among the most toxic antitumor antibiotics described to date. One would have been motivated to do so because Trail et al. teaches that antibody-directed delivery of calicheamicin provides a potential means to exploit this impressive potency while minimizing their systemic toxicity. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering a conjugate comprising calicheamicin and an anti-CD22 antibody, one would achieve an effective method of treating a B-cell malignancy.

Note: In order to expedite prosecution, the Examiner would like to address Applicants arguments pertaining to the previous rejection as they relate to the instant rejection. In response the previous rejection, Applicants would like to first point out that because independent claim 124 was not rejected by the Examiner as obvious under 35 USC 103(a), and claims 128 to 130 and 134 depend from claim 124 and incorporate all of the elements of claim 124, Applicants respectfully submit that the rejection of claims 128 to 130 and claim 134 are improper. Moreover, Applicants assert that the Examiners reading of Goldenberg's definition (citing col. 13, lines 29-63) of an immunoconjugate as an antibody conjugated with a therapeutic agent is mistaken. For example, Applicants contend that in column 11, lines 5-7 Goldenberg states that preferred immunoconjugates include radiolabelled antibody components or conjugates of an anti-CD22 antibody component and

an immunomodulator. With regards to the immunomodulator, Applicants assert that Goldenberg et al. teach that the immunomodulators include cytokines, stem cell growth factor, toxin, hematopoietic factor, colony stimulating factor, granulocyte macrophage-colony stimulating factor or an interferon (see col. 11, lines 5-6 and 41-53). Thus, Applicants assert that cytotoxic drugs are not included in the definition of an immunomodulator in Goldenberg. In addition, Applicants assert that Goldenberg et al. does not teach administration of an anti-CD22 antibody immunoconjugate with an anti-CD19 naked antibody/immunoconjugate or anti-CD20 naked antibody/immunoconjugate. For example, Applicants assert that Goldenberg clearly states that the patients receive "naked anti-CD22 antibodies", not immunoconjugates, supplemented with administration of an anti-CD19 naked antibody or anti-CD19 immunoconjugate or anti-CD30 naked antibody or anti-CD20 immunoconjugate (col. 13, lines 29-33). Applicants further contend that the Examiner statement with regards to Trail et al. teach that antibody directed delivery of calicheamicin provides a potential means to exploit the potency of these compounds while minimizing their systemic toxicity (emphasis added) is merely providing a "suggestion to try" and provides no motivation to make the cytotoxic drug-anti-CD22 antibody conjugate.

These arguments have been carefully considered, but are not found persuasive.

First, the Examiner would like to apologize for any confusion the previous rejection caused with respect to Claim 124. In the instant case, the Examiner acknowledges that claim 124 was not included in the "first" sentence of the 103 rejection, but recognizes that the previous claim 124 was included in the 102 rejection as being anticipated by Goldenberg. As such, it would flow logically that if claim is anticipated with would therefore be obvious. Regarding Applicants assertions that Goldenberg et al. does not include, cytotoxic molecules in the teachings of the antibody conjugate, the Examiner acknowledges and agrees with Applicants that in one preferred embodiment Goldenberg et al. teach that preferred immunoconjugates include radiolabelled antibody components or conjugates of an anti-CD22 antibody component and an immunomodulator such as cytokines, stem cell growth factor, toxin, hematopoietic factor, colony stimulating factor, granulocyte macrophage-colony stimulating factor or an interferon . However, the Examiner recognizes that Goldenberg et al. clearly teach that an immunoconjugate is a conjugate of an antibody component with a therapeutic agent, wherein the therapeutic agent includes drugs, toxin, immunomodulators, chelators, boron compounds, photoactive agents or dyes, and radioisotopes

(column 4, liens 15-17 and 25-26). In particular, the Goldenberg et al. teaches that useful cancer chemotherapeutic drugs for the preparation of immunoconjugates include nitrogen mustards, alkyl sulfonates, nitrosureas, triazenes, folic acid analogs, pyrimidine analogs, purine analogs, antibiotics, epipodophyllotoxins, platinum coordination complexes, hormones, and the like (column 12, lines 61+). In the instant case, Applicants are reminded that a reference, in particular patents, may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Regarding Applicants contention that Goldenberg et al. does not teach administration of an anti-CD22 antibody immunoconjugate with an anti-CD19 naked antibody/immunoconjugate or anti-CD20 naked antibody/immunoconjugate, the Examiner acknowledges and concedes that Goldenberg et al. does not specifically teach administration of an anti-CD22 antibody conjugate in combination with an anti-CD19 naked antibody/immunoconjugate or anti-CD20 naked antibody/immunoconjugate. However, The examiner recognizes that Goldenberg et al. clearly teaches administration of the anti-CD22 immunoconjugate with a naked anti-CD22 antibody for the treatment of B-cell related malignancies. As such, Goldenberg et al. clearly teaches administration of a cytotoxic drug-anti-CD22 antibody conjugate with one or more biologically active agents such as an antibody which binds to a cell having an antigen expressed on B-cell malignancies. Lastly, regarding Applicants contention that the Examiners statement with respect to Trail et al. is a "suggestion to try" and provides no motivation to combine, the Examiner recognizes that The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the ad (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969).

Claims 134-135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldenberg (US 6,183,744, 2001) in view of Trail et al. (Current Opinion in Immunology 1999, 11: 584-588, of record), as applied to claims 113-121, 124-127, 129-133 and 142-143 above, and in further view of Maloney et al. (Blood 1997; 90: 2188-2195).

Goldenberg in view of Trail et al. teaches a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a calicheamicin derivative.

Goldenberg in view of Trail et al. does not explicitly teach that the immunoconjugate is administered in combination with Rituximab, an anti-CD20 antibody.

Maloney et al. teach a method of treating low-grade Non-Hodgkin's lymphoma, comprising administering to a patient in need thereof a therapeutically effective amount of Rituximab (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of treating Non-Hodgkin's lymphoma comprising administering an immunoconjugate comprising an anti-CD22 antibody as taught by Goldenberg in view of Trail et al. with Rixuximab in view of Maloney et al' teachings that Rituximab is effective at treating Non-Hodgkin's lymphoma because each of the agents have been individually taught in the prior art for the treatment of lymphoma. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have a reasonable expectation of success that by administering a immunoconjugate comprising an anti-CD22 antibody in combination with Rituximab, one would achieve an effective method of treating a B-cell malignancy.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have

been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

Claims 145-149 appear to be free of the prior art, but are objected to for being dependent from a rejected independent claim.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600